REPLY

Dr. Ghali may be expecting too much from post hoc subgroup analysis of clinical trial data (1). The sample size in the low blood pressure subgroup (n = 132) is too small to offer any power to detect a difference in hazard ratio from the other subgroups. Furthermore, far fewer patients in the low blood pressure subgroup were at target dose of carvedilol and far more were permanently discontinued because of adverse effects. Indeed, the similar benefit of carvedilol in this subgroup despite the lower compliance with the drug regimen supports the suggestion that the drug, if tolerated, has a striking benefit in this population.

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REPLY

In his letter, Dr. Ghali notes that one may expect patients with heart failure and the lowest systolic blood pressure, those at highest risk, to enjoy a higher relative benefit from the use of carvedilol. Indeed, in the COPERNICUS study (1), patients with the lowest systolic blood pressure were at highest risk. We did not, however, identify a greater relative benefit with carvedilol. Dr. Ghali invites us to speculate as to why a greater relative benefit was not found. At least four possibilities exist.

First, because patients with the lowest systolic blood pressure had the greatest rate of discontinuation of carvedilol, and less frequently achieved target dose, it is possible that, if one corrected for adherence and dose, these patients indeed did derive a greater relative benefit from carvedilol, when they could tolerate a target dose. Alternatively, as the relative benefit of bisoprolol (2) and controlled release metoprolol (3) in patients with somewhat less severe heart failure was found to be comparable to that of carvedilol in patients with more severe heart failure, it may be that the relative benefit of beta-blockers is independent of the severity of heart failure.

A third possibility is that a relatively greater direct benefit of carvedilol in patients with the lowest systolic blood pressure was masked by greater indirect risk associated with excessive hypotension due to the combined vasodilator and beta-blocking effects of carvedilol. Whatever the explanation, our study was not powered to find a difference in subgroups, such that a true beneficial interaction between systolic blood pressure and carvedilol may have been missed. Against this possibility is the lack of any trend in favor of a greater relative benefit in patients with lower systolic blood pressure randomized to carvedilol.

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Should the Lack of Feasibility of Conducting Controlled Trials Influence Evidence-Based Guidelines?

The expert panel/writing group presented evidence-based guidelines for cardiovascular disease prevention in women (1). The researchers stated it is appropriate to consider supporting class I recommendations with level-B evidence when there is lack of feasibility of conducting future controlled studies in women. This method of handling incomplete data constitutes a clear departure from a pure evidence-based system wherein the lack of evidence, for whatever reason, weakens the truth value of an issue and should therefore lead to less strong recommendations. Moreover, this new approach is ironic given that the hormone replacement therapy observational data was only found to be incorrect by appropriate controlled trials. Allowing incomplete data to support class I recommendations may give the appearance that further studies are not necessary. One can reasonably argue that, although ethical or practical reasons may exist not to conduct randomized trials, there is rarely a pure scientific reason not to do so. To the contrary, such trials are mandated if cause and effect are to be appropriately assessed. Even if the cited issues regarding cigarette smoking in women arguably justify separate handling of pertinent recommendations, it is not at all clear whether such a move can be justified for the other lifestyle recommendations. I have previously argued (2) that the single hierarchy system currently used to evaluate the evidentiary merit of cardiovascular guideline recommendations may be misleading in the real world, particularly with respect to opinion evidence. The expert panel's (1) current departure from traditional scientific evidence further supports such a revision of the current single hierarchy evidentiary system. If panel members wish to assign a stronger truth value to certain evidence under "justifiable" circumstances they should do so outside the evidence-based single hierarchy system. As such, the statement could be made for ethical reasons without degrading the concept of scientific evidence.

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